CONG

Challenges with heparin-based anticoagulation during cardiopulmonary bypass in children: Impact of low antithrombin activity

Cedric Manlhiot, PhD,[a] Colleen E. Gruenwald, MHSc, CCP, PhD,[a] Helen M. Holtby, MB, BS,[a] Leonardo R. Brandão, MSc, MD,[b] Anthony K. Chan, MD,[c] Glen S. Van Arsdell, MD,[a] and Brian W. McCrindle, MPH, MD[a]

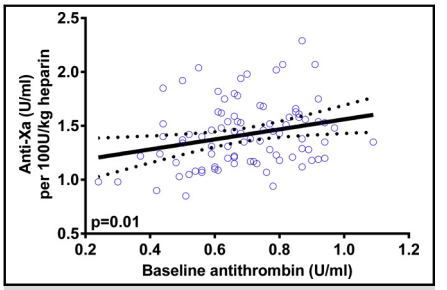
ABSTRACT

Background: Antithrombin is one of the main natural coagulation system inhibitors. It is potentiated by heparin, and may be a key component of heparin response, particularly in infants aged <1 year. We sought to determine the impact of baseline antithrombin activity on response to heparin and thrombin generation during cardiopulmonary bypass (CPB).

Methods: Secondary analysis was performed using linear regression analyses, which combined patients from a trial of individualized versus weight-based heparin management for 90 infants aged <1 year undergoing cardiac surgery.

Results: Mean baseline antithrombin activity was 0.69 ± 0.16 U/mL, and it was lower in neonates than in older infants (0.57 ± 0.15 vs 0.77 ± 0.12 U/mL; $P < .001$). Lower baseline antithrombin activity was associated with lower post-heparin anti-Xa activity (EST [SE]: +0.47 (0.19) U/mL per 100 U/kg heparin; $P = .01$) and higher heparin doses during surgery (EST [SE]: +51 (17) U/kg per hour; $P = .003$). The administration of fresh frozen plasma attenuated the effect of low baseline antithrombin activity (interaction P value = .009). Patients with lower anti-Xa activity recorded during CPB had higher levels of thrombin-antithrombin complex (EST [SE]: +12.8 (4.7) ng/mL per −1 U/mL anti-Xa; $P = .006$); prothrombin activation fragment 1.2 (EST [SE]: +0.13 (0.07) log pg/mL per −1 U/mL anti-Xa; $P = .06$); and D-dimer (EST [SE]: −0.25 (0.09) log ng/mL per −1 U/mL anti-Xa; $P = .009$) in the postoperative period after adjustment for baseline antithrombin activity, duration of CPB, amount of fresh frozen plasma and heparin used throughout surgery in multivariable models.

Conclusions: Low circulating antithrombin activity is associated with lower heparin efficacy, which ultimately leads to a lower ability to suppress thrombin generation during CPB. Determination of risk factors for heparin resistance, and potentially, antithrombin replacement therapy, may individualize and improve anticoagulation treatment. (J Thorac Cardiovasc Surg 2016;151:444-50)



Low preoperative blood antithrombin activity is associated with decreased heparin response.

Central Message

Low blood antithrombin is associated with lower heparin efficacy and a lower ability to suppress thrombin generation during neonatal cardiac surgery.

Perspective

Low preoperative blood antithrombin activity in neonatal cardiac surgery was associated with decreased heparin efficacy and increased thrombin generation. Strategies to normalize blood antithrombin levels before heparinization should be investigated further. In the meantime, intraoperative anticoagulation dosing should be adjusted to reflect preoperative blood antithrombin levels.

See Editorial page 305.

Anticoagulation using heparin is challenging in children, particularly in infants, yet it is necessary in many clinical situations.[1,2] Challenges associated with heparin therapy in children are multifactorial but include altered pharmacodynamics and greater between-patient variability. There is a lower dose response and increased rate of

From the [a]Labatt Family Heart Centre, Department of Pediatrics; [b]Division of Haematology/Oncology, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto; and [c]Division of Pediatric Hematology/Oncology, Department of Pediatrics, McMaster University, McMaster Children's Hospital, Hamilton, Ontario, Canada.

Funding for the original trial was provided by the Heart and Stroke Foundation of Ontario, Canada (NA5917).

Read at the American Heart Association Scientific Sessions, Chicago, Illinois, November 16-19, 2014.

Received for publication July 1, 2015; revisions received Sept 24, 2015; accepted for publication Oct 1, 2015; available ahead of print Nov 6, 2015.

Address for reprints: Brian W. McCrindle, MPH, MD, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (E-mail: brian.mccrindle@sickkids.ca).

0022-5223/$36.00

Copyright © 2016 by The American Association for Thoracic Surgery

http://dx.doi.org/10.1016/j.jtcvs.2015.10.003

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
EST = parameter estimate
FFP = fresh frozen plasma

Scanning this QR code will take you to the article title page.

clearance than in adults resulting in decreased effectiveness in preventing thrombin generation.[3,4] Heparin is used throughout cardiopulmonary bypass (CPB) to counteract the physiologic response to CPB and mitigate the risk of thrombosis. Improving heparin-based anticoagulation is particularly important in children who have heart disease, who often require multiple surgical interventions at a very young age and are at high risk of postoperative thrombosis[5-10] and bleeding complications,[1,11-13] partially owing to physiologic and maturational differences that exacerbate the adverse effects of CPB. A previous retrospective review of children undergoing cardiac surgery noted an 11% prevalence of postoperative thrombosis, and a 12% prevalence of postoperative bleeding complications (>25% for both in children aged <1 year; <2% in children age >10 years).[10]

One of the reasons for the differences in heparin sensitivity between patients (and between children and adults) may be related to the anticoagulation activity of antithrombin which is potentiated by heparin.[14] Heparin covalently bonds to antithrombin and induces a conformational change in the protein structure that profoundly increases the anticoagulant activity.[15] The activity of antithrombin is highly variable and can be influenced by age, inflammation, heart failure, and liver dysfunction.[5,16,17] We sought to determine the effect of low preoperative antithrombin activity on the response to heparin and anticoagulant effectiveness in infants age <1 year undergoing cardiac surgery with CPB. Our secondary objective was to determine the association between anticoagulation effectiveness, as reflected by the anti-Xa associated with heparin, and thrombin generation and fibrin-degradation byproduct activity after surgery.

METHODS

A secondary analysis was performed of data derived from a controlled trial of 90 patients who were randomized to weight-based versus individualized management of heparin and protamine dosing in children aged <1 year undergoing cardiac surgery with CPB.[18] Complete methods and results of the trial have been published,[18] and relevant methodologic considerations are addressed later. In short, we showed that individualized heparin and protamine dosing using the Hepcon HMS Plus Hemostatis Management System (HMS; Medtronic, Minneapolis, Minn), with a locally developed pediatric-specific algorithm, was associated with improved surgical outcomes, compared with patients receiving heparin on a weight-based dosing algorithm with periodic monitoring. Patients receiving individualized heparin and protamine dosing had more-stable anticoagulation activity throughout CPB; reduced postoperative activity of thrombin-antithrombin complex and prothrombin fragment F1.2, reduced need for blood transfusions; and reduced ventilation, intensive care unit, and hospital stay. Baseline antithrombin activity was not different between the 2 experimental groups in the original study, and no additional analyses of antithrombin association with anticoagulant and operative outcomes were included in the original publication.

All patients had to weigh >2 kg at surgery and age adjusted for number of weeks of gestation at birth had to be >36 weeks. Patients were eligible if they had no preoperative anticoagulation exposure, no previous antithrombin replacement therapy, no major previous bleeding and/or thrombotic complications, and no history of renal and/or liver failure. Other than the heparin and protamine management, all patients were treated in the same manner with respect to perioperative and postoperative blood transfusion protocols and use of antifibrinolytic agents.

All patients had hemostasis monitoring before, during, and after surgery (blood antithrombin activity, blood hemostasis, and complete blood count). All laboratory investigations during CPB were performed every 30 minutes; however, for the purpose of this study, only the last measurement on CPB was considered. Postoperative measurements were performed 24 hours after arrival at the critical care unit. All patients were monitored using the hemostasis management device (these data were not made available to physicians for patients allocated to the weight-based heparin management group). Measurements of blood antithrombin activity, blood hemostasis, complete blood counts, anti-Xa activity, and D-dimers were performed in a central clinical laboratory.

Measurements of thrombin-antithrombin complex and prothrombin fragment were used to quantify thrombin generation. Measurements were performed using the Enzygnost thrombin-antithrombin complex and prothrombin fragment monoclonal assays (Siemens, Marburg, Germany). Several metrics were used to characterize heparin efficacy including the initial anti-Xa activity achieved per 100 U/kg of heparin in the pre-CPB bolus given to each patient, and the total amount of heparin used, indexed to patient weight and duration of CPB.

Both original study groups were combined for this secondary analysis. Data are presented as means with SDs, medians with 25th and 75th percentiles, or frequencies, as appropriate. Primary analyses were performed using linear regression models (both univariable and multivariable models), with maximum likelihood estimates for parameter estimation. Results from regression models are reported as parameter estimates (ESTs) and standard errors (SEs); ESTs represent the change in the dependent variable for each increase of 1 unit in the independent variable (if continuous) or for the presence (vs absence) of the dependent variable (if binary), as appropriate.

Given the limits of the sample size and the need for biologically relevant adjustments, we elected to use an a priori selection of covariates as part of our model-building strategy, rather than a data-driven approach, to make sure that all biologically important covariates were adjusted for, without overfitting the regression models. The strong correlation between age at surgery and antithrombin activity, along with the limited number of patients at the higher end of the age spectrum with low antithrombin activity, precluded using age at surgery as a covariate. Covariates specific to each regression model are listed at the appropriate location in the Results section.

Although no differences were found between study groups in the original trial regarding baseline antithrombin activity, patients in the HMS group had different heparin management, improved anticoagulation, decreased thrombin generation, and improved clinical outcomes. Given

Download English Version:

https://daneshyari.com/en/article/2978973

Download Persian Version:

https://daneshyari.com/article/2978973

Daneshyari.com